## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 21, 2010 has been entered. Applicants' arguments have been fully considered but they are not deemed to be fully persuasive. The following rejections and/or objections constitute the complete set presently being applied to the instant application.

### *Claim Rejections - 35 USC § 103*

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

4. Claims 1, 11, 13, 16, 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bissett et al .(WO 95/24785). This rejection is maintained for the reasons set forth herein.

Bissett et al. discloses an emulsion composition comprising 1,2-dimethyl-3-hydroxy-pyrid-4-one (deferiprone) that is applied to twice daily to the skin (p 16, ln 8 – 29). Pharmaceutically acceptable salts of the active ingredient can also be used (p 2, ln 3 – 8). The active ingredient are iron chelating compounds that reduce the level of free radicals in mammalian cells (p 1, ln 8 – 10). It is believed that the compounds bind to iron in such a way so that the iron cannot participate in the formation of radical species (p 2, ln 14 – 18). The potential for damage by free radicals is greatly increased by the presence of iron that catalyzes the conversion of the free radicals to less stable and therefore more reactive species (p 1, ln 15 – 17).

Bissett et al. does not disclose the topical administration of the deferiprone composition to patients suffering a microcirculatory disorder such as rosacea and therefore are in need of treatment for a microcirculatory disorder.

Perricone discloses that patients with rosacea, a chronic inflammation disorder affecting the blood vessels of the face, suffer from papule and pustules superimposed on diffuse erythema and telangiectasia (visible blood vessels) over the central portion of the face (¶ [0004]). The treatment of rosacea is the topical application of a composition

comprising lipoic acid (¶ [0019]). Lipoic acid has been suggested for the treatment of inflammation and aging of the skin as because of its antioxidant activity, as it appears to prevent free radical damage (¶ [0015]).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to topically apply deferiprone to a patient suffering from rosacea and/or telangiectasia. One of ordinary skill would have been motivated and reasonably would have expected success as Bissett et al. teaches that topical application of deferiprone decreases free radicals by way of iron chelation in the skin and Perricone teaches that rosacea and telangiectasia can be treated by topical application of an agent which decreases free radicals. Whether by direct action as an antioxidant and/or by chelation of iron to decreased the potential damage caused by free radicals that are generated, the rosacea and/or telangiectasia will be ameliorated, leading to treatment of the skin microcirculatory disorder.

Applicant traverses this rejection on the grounds that the Examiner has not provided any evidence that all agents that reduce free radical damage would work to treat SMD. Absent evidence to the contrary, the skilled worker would not expect agents that are know to reduce free radical damage would work as well as (or the same as) an agent that is also an iron-chelator in treating SMD.

These arguments are unpersuasive. It is not required that all agents that reduce free radical damage will treat SMD in order to establish a *prima facie* case of obviousness. Based on the combined teachings of the applied prior art, a reasonable

expectation of success in the treatment of a SMD with deferiprone is present. Bissett et al. teaches that by chelating iron with a compound such a deferiprone will decrease the amounts of free radicals that react with the iron to generate even more reactive free radical species. Perricone teaches that rosacea and telangiectasia can be treated by topical application of an agent which decreases free radicals. Therefore, the person of ordinary skill in the art would have a reasonable expectation of success that deferiprone will ameliorate rosacea and/or telangiectasia.

Applicants also argue that Perricone does not disclose hydroxypyridinone compounds or that lipoic acid is an iron chelator.

This argument is unpersuasive. The teachings of hydroxypyridinone compound of deferiprone is provided by Bissett. It is not necessary that lipoic acid be an iron chelator in order for the references to be combined – deferiprone and lipoic acid are each taught in the respective references to be antioxidant and in the same field of topical treatment of skin conditions.

5. Claims 1, 3 – 6, 11 – 14, 16, 19 and 20 were rejected under 35 U.S.C. 103(a) as being unpatentable over Ghisalberti et al. (WO 01/17497) in view of DermNet NZ entries for capillaritis, cutaneous vasculitis and purpura (accessed 2/19/08, provided with March 4, 2008 Office Action).

Ghisalberti teaches compositions which are useful for the treatment of hyperpigmented skin (p 1, ln 6 – 8). Hyperpigmentation of the skin can result from increased melanin, but also the presence of other pigments such as hemosiderin that is

present in the patients who were treated with deferiprone after undergoing sclerotherapy (p 25, ln 21). Pigmentative hemosiderin deposits are formed when hemoglobin (in blood that escapes the blood vessel) binds to dermal and connective proteins, stimulating the activity of melaoncytes (p 3, ln 7 – 24). Substances such as the 3-hydrocypyr(id)one compound deferiprone depigment hyperpigmented skin that has manifested itself as spots, or larger area of a dark color, either due to an excess of melanin and/or to hemosiderinic deposits (p 5, ln 11 – 16). Application of these compounds treats or prevents melanin spots of different origin but also reduces and/or completely whiten hemosiderin spots (p 5, ln 17 – 19). This dual action makes these compounds particularly useful to whiten or depigment the skin (p 8, ln 12 – 15). The compounds are administered in the form of a topical composition (p 8, ln 22 – p 9, ln 2). Local application to the skin is employed, preferably with soft massage to enhance penetration of the cosmetic active ingredients (p 15, ln 16 – 18). Example 3 is a composition containing deferiprone for the melasmas on limb (p 22, ln 4 – 11).

Ghisalberti does not disclose the use of these compounds for treating other skin conditions such as rosacea or purpura.

Purpura is a generic name for the discoloration of the skin caused by bleeding from small blood vessels that have a variety of causes (p 1, DermnetNZ entry for "purpura", accessed 2/19/2008). One type of purpura, pigmented purpura, is also known as capillaritis (p 1, DermnetNZ entry for "capillaritis", accessed 2/19/2008). As disclosed in the instant specification, capillaritis encompasses a variety of conditions, including several types of purpura (Schamberg's disease, purpura annularis telangiectodes,

itching purpura and pigmented purpuric lichenoid dermatosis) and lichen aureus (p 6, ln 15 – 20). Cutaneous vasculitis refers to an inflammation of blood vessels in the skin (p 1, DermnetNZ entry for "cutaneous vasculitis", accessed 2/19/2008) that, in its acute stage, presents with bleeding under the skin (purpura; p 3). Rosacea is a disease that is characterized by blotchy red areas of the skin that results from vessel leakage (p 1, ln 19 – 22 of the instant specification). All of these conditions are characterized by the presence of blood outside the blood vessels.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to treat skin disease characterized by the presence of blood outside of blood vessels by the topical application of deferiprone. The person of ordinary skill in the art would have been motivated to make those modifications and reasonably would have expected success because Ghisalberti et al. discloses that hemosiderin spots for when hemoglobin contact dermal and connective tissue, which can also lead to activation of the melanocytes. Deferiprone can depigment skin that has been hyperpigmented by the presence of excess melanin and hemosiderinic deposits.

Applicants traverse this rejection on the grounds that Ghisalberti only deals with the treatment of hyperpigmented skin. The pathologies of the claimed SMD are not in any way related to the production of melanin resulting in hyperpigmentation. Spots that are hemosiderinic in nature do not arise from microcirculatory bleeding.

These arguments are unpersuasive. As shown in the discussion above, the disclosure of Ghisalberti is not solely related to hyperpigmentation caused by melanin

production. Hemosiderin deposit and the mechanism of such formation caused by contact of hemoglobin with dermal and connective tissue is clearly disclosed. Nothing in the art or the knowledge of one of ordinary skill in the art indicates that mechanism by which the blood leaves the blood vessel (e.g., needle puncture of the vascular system, a bruise or other leakage of the blood vessels) will not lead to the formation of hemosiderin deposits when the hemoglobin contacts the dermal and connective tissue. Applicants provide no citations or other evidence to back up the statement that "[s]pots that are hemosiderinic in nature do not arise from microcirculatory bleeding." Arguments without factual support are mere allegations and are not found persuasive.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NISSA WESTERBERG whose telephone number is (571)270-3532. The examiner can normally be reached on M - F, 8:00 a.m. - 4 p.m. ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nissa M Westerberg/
Primary Examiner, Art Unit 1618